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AB 1. The lipid soluble extract of the psychoactive beverage kava has hypnosedative properties which can be measured by the length of time that the righting reflex is lost. 2. Ethanol and the lipid soluble extract (kava resin) have been shown greatly to increase each others hypnotic action in mice. Ethanol also increases the toxicity of kava markedly. 3. This interaction of kava and alcohol has important clinical and social consequences since, in contrast to traditional usage, kava is now often taken in conjunction with alcoholic drinks.

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POSITIVE INTERACTION OF ETHANOL AND KAVA RESIN IN MICE

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SUMMARY

1. The lipid soluble extract of the psychoactive beverage kava has hypnosedative properties which can be measured by the length of time that the righting reflex is lost.

2. Ethanol and the lipid soluble extract (kava resin) have been shown greatly to increase each others hypnotic action in mice. Ethanol also increases the toxicity of kava markedly.

3. This interaction of kava and alcohol has important clinical and social consequences since, in contrast to traditional usage, kava is now often taken in conjunction with alcoholic drinks.

Key words: alcohol, ethanol, kava sedation, toxicity.

INTRODUCTION

The psychoactive properties of kava, the traditional drink throughout much of the South Pacific, has been known for centuries. Initially this non-alcoholic beverage, produced from the plant *Piper methysticum*, was drunk mainly on ceremonial occasions, and sometimes on social occasions. However, in recent years kava has been abused by some Aboriginal communities in Australia (Cawte 1986), with the consumption of very large doses. In addition, and in contrast to previous practice, kava is now often drunk in conjunction with alcohol (Cawte 1988; Gerrard 1988; Rothwell 1988). However, no studies have been undertaken, in animals or humans, to ascertain whether there are interactions between kava and alcohol. Thus in the present investigations we have studied the effects of the pharmacologically active lipid soluble extract of kava (Meyer, 1962; Keller & Klohs 1963; Hänsel 1968; Shulgin 1973) on sleeping times (hypnosis) in mice, both alone and in combination with alcohol.

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METHODS

Male Balb/c mice 20–25 g bodyweight) were used in these experiments. After dosing, animals were placed in a 32°C heated chamber, and carefully observed. Sleeping times (hypnosis) in these experiments were recorded as the time from the loss of the righting reflex to regaining of the righting reflex, with minimal interference from the operator during the test.

Drugs and administration

The lipid soluble extract of kava (kava resin) was prepared exactly as described previously (Jamieson *et al.* 1989). The extract was administered orally, in 5% cremefor-EL in saline for doses at or below 300 mg/kg. For more concentrated kava solutions (used for doses above 300 mg/kg) it was necessary to use 10% cremefor in saline as the vehicle. Alcohol (ethanol, CSR, Australia) was administered intraperitoneally (i.p.), diluted with saline to deliver a volume of 0.1 mL/10 g bodyweight. Various doses of each substance were used, as described under Results. For experiments where both drugs were given kava resin was administered orally 2 min before i.p. injection of ethanol. Control mice received equivalent volumes of vehicle as required.

Statistical Evaluation

All results are shown as mean and s.e.m. Student's unpaired *t*-test was used to calculate significance levels in this study.

RESULTS

Effect of kava resin on ethanol-induced hypnosis

Several doses of ethanol were tested in preliminary experiments. A dose of 3 g/kg failed to cause loss of the righting reflex in five out of five mice. A dose of 3.5 g/kg produced hypnosis (Fig. 1) and the length of the sleeping time increased sharply as the dose was raised

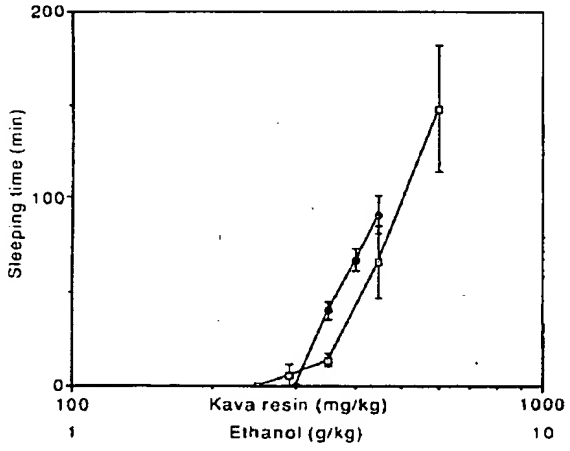

Fig. 1. Log dose–response curves for ethanol (●) and kava resin (⊡).

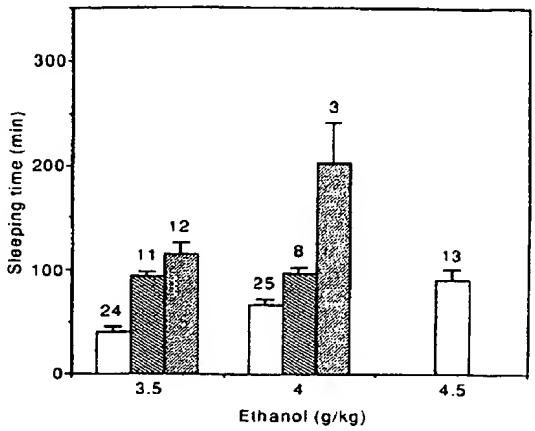

Fig. 2. The effect of subhypnotic doses of kava resin on sleeping time of mice treated with hypnotic doses of ethanol; 200 mg/kg kava resin (▨), 300 mg/kg kava resin (▨), and ethanol alone (□). The number of animals in each group is shown.

to 4 g/kg then 4.5 g/kg. This latter dose killed one of 14 mice, and above this dose toxicity was too high to determine sleeping times.

From Fig. 2 it can be clearly seen that the kava extract greatly increased alcohol hypnosis. A dose of 200 mg/kg of kava resin caused a highly significant ($P<0.001$) increase in the sleeping time of mice injected with 3.5 g/kg or 4 g/kg of ethanol. Increasing the kava resin dose to 300 mg/kg further prolonged the hypnosis induced by 3.5 g/kg or 4 g/kg ethanol and indeed the sleeping times with these combinations were in excess of those which could be achieved with ethanol alone, as the toxicity of ethanol was too high, above 5 g/kg, to obtain sleeping time data. However it must be pointed out that 300 mg/kg kava also proved lethal to three of the six mice treated with 4 g/kg ethanol, indicating that toxicity as well as hypnosis was increased.

Effect of ethanol on kava resin induced hypnosis

Preliminary studies showed that no loss of the righting reflex was produced by doses of kava resin below 200 mg/kg, administered orally. Doses of kava between 250 and 300 mg/kg caused a short-term loss of the righting reflex in four of eight mice (Fig. 1). At 350 mg/kg consistent loss of the righting reflex occurred, and sleeping times increased as the kava resin dose was raised to 600 mg/kg (Fig. 1). One of six mice died at this latter dose and lethality was greater than 50% at and above 700 mg/kg. The doses of kava resin to produce loss of the righting reflex and toxicity in this present study were thus somewhat higher than that found previously (Jamieson *et al.* 1989), probably reflecting differences in potency between various batches of the lipid soluble extract. The ratio of toxicity to activity remained similar, however.

A dose of 1 g/kg ethanol did not alter the sleeping times of mice injected with either 350 or 450 mg/kg kava (results not shown). However, it can be seen that 2 g/kg of alcohol greatly prolonged the mean sleeping time produced by 350 mg/kg kava ($P<0.001$) and this effect could be further increased as the dose of ethanol was raised to 3 g/kg (Fig. 3).

The interaction of ethanol and kava was more difficult to study when 450 mg/kg kava resin was used to induce hypnosis, due to toxicity. Thus administration of 2 g/kg of ethanol

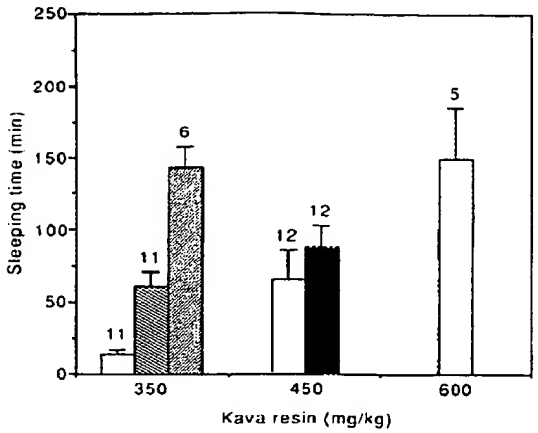

Fig. 3. The effect of subhypnotic doses of ethanol on hypnosis produced by kava resin; 1.5 g/kg ethanol (■), 2.0 g/kg ethanol (▤), 3.0 g/kg ethanol (▨) and kava resin alone (□).

plus 450 mg/kg of resin quickly killed three of five mice and one further mouse showed respiratory difficulty but did regain its righting reflex at about 180 min. The remaining animal regained the righting reflex at 160 min. Decreasing the ethanol dose to 1.5 g/kg failed to significantly increase sleeping time (Fig. 3).

DISCUSSION

In 1959 Hänsel and Beiersdorff reported that two of the pharmacologically active α-pyrones from the lipid soluble extract of kava (kava resin), namely dihydrokawain and dihydromethysticin, could induce hypnosis in mice and rats. In the same year Klohs *et al.* (1959) described a marked prolongation of the pentobarbitone-induced sleeping time of mice by either the lipid soluble extract or several of the α-pyrones derived from this extract. These results were confirmed by Meyer (1962) for dihydrokawain and dihydromethysticin, using potentiation of hexobarbitone sleeping times in mice and rabbits.

On the basis of these results it may be expected that a positive interaction between alcohol and kava would occur, as alcohol also has hypnosedative properties and many previous studies have demonstrated positive deleterious interactions between alcohol and other hypnosedative drugs, such as diazepam (Linnoila & Mattila 1973; Morland *et al.* 1974; MacLeod *et al.* 1977; Palva *et al.* 1979).

The present investigations prove that indeed an interaction of considerable magnitude does exist between ethanol and kava resin. Superficially this interaction appears to be much greater than additive but it may be illusory to claim that these agents greatly potentiate each other's actions. As pointed out by Palva *et al.* (1979) for diazepam-alcohol treatments, it is important to consider the dose–response relationships of the individual agents when analysing drug interactions. For example the benzodiazepine midazolam reduces cerebral blood flow and oxygen consumption and the dose–response curve for this effect is very flat (Gorder *et al.* 1985). Ethanol increases the effect of midazolam by about 50%, yet this

corresponds to a 10-fold increase in midazolam dose. A steep dose–response relationship was found for kava resin in the present, as well as in previous investigations (Duffield *et al.* 1989; Jamieson *et al.* 1989; Jamieson & Duffield 1990). Ethanol also produced a steep dose–response graph, and, as far as can be ascertained from the limited number of data points, the dose–response relationships for kava resin and ethanol are very similar. They are also similar to the steep dose–response curves obtained for barbiturate-induced sleeping times (Meyer 1962). Thus a dose of 3 g/kg ethanol, ineffective alone, caused a very large (10-fold) prolongation of the mean sleeping time of mice treated with a minimally effective hypnotic dose of kava resin (350 mg/kg). The duration of hypnosis produced by this combination of doses corresponds to about 600 mg/kg kava resin given alone. A similar pattern was seen when subhypnotic doses of kava resin were administered with hypnotic doses of ethanol. Very large increases in sleeping times occurred; for example, 300 mg/kg kava resin caused a three-fold prolongation of the sleeping times induced by ethanol. This would correspond to a 1.5-fold shift to the left of the ethanol dose–response curve (Fig. 1). Thus very large increases in effect, as seen in the present experiments, can correspond to considerably smaller dose increments when dose–response curves are very steep. Thus we prefer to use the term positive interaction rather than potentiation for the effects seen in our experiments.

In addition to their hypnotic interaction, kava and ethanol increased each other's toxicity; an effect particularly evident when ethanol was combined with effective doses of kava resin. Thus while the addition of up to 1.5 g/kg ethanol did not significantly increase the duration of hypnosis caused by 450 mg/kg of kava resin (approximately the ED50), the combination of 2 g/kg ethanol plus this dose of resin was lethal in three of five mice. In agreement with earlier studies using the lipid soluble components of kava (Meyer 1962; Kretzschmar *et al.* 1970; Jamieson *et al.* 1989) a relatively low therapeutic index was found for kava resin in the present investigation, and thus any exacerbation of the toxicity of kava must be treated seriously. The increased toxicity of the kava-ethanol combination is not unexpected as ethanol is known to increase the lethality of other sedative drugs, including benzodiazepines (Etzler *et al.* 1969) and barbiturates (Burner 1967). Yet Meyer (1962) reported very marked increases in the sleeping times with no accompanying increase in toxicity, when the kava pyrones dihydromethysticin or dihydrokawain interacted with hexobarbital sodium. This latter result is somewhat surprising and is certainly in marked contrast to our results for the kava-ethanol interaction.

Altogether, the positive interactions between ethanol and kava resin described in our experiments have important implications, both clinically and socially, as kava, traditionally drunk by itself, is now frequently consumed in combination with alcohol. This is particularly prevalent amongst some of the Australian Aboriginal communities (Cawte 1988; Gerrard 1988; Rothwell 1988). Even more potentially dangerous is the reported mixing of the kava beverage with spirits or 'even adulterating the kava powder base' (Rothwell 1988). In the latter case not only can the pharmacological effects of both drugs be greatly increased, but also considerably more of the active pyrones may be extracted and remain in the drink than when the powder is made up in the usual way, with water.

ACKNOWLEDGEMENTS

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